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Particularities regarding Clinical-biological and Evolutive Parameters of Immune-mediated Rheumatic Diseases in Patients with COVID-19 – systematic literature review

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Abstract: Background: Since its outbreak in 2019, Coronavirus disease 2019 (COVID-19)/Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was a serious medical threat and was declared Global Pandemic, triggering fear, panic and uncertainty for people around the Globe. Among those individuals, there is a specific category of patients – the ones with immune-mediated rheumatic diseases (IMIDs) – whose mantra from the diagnosis was to avoid infections at all costs because of the additional negative impact on the immune system and overall reactivity. **Objective**: Considering the aforementioned, our objective is to understand the in-depth relation of the immune system of patients with IMIDs in the setting of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and the real burden of the disease and vaccination against COVID-19. **Materials and Methods:** In this respect, we have conducted a thoroughly systematic literature review according to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" concept. Following its five-steps algorithm, we first selected 745 articles that were published in reputable international medical databases, ISI-indexed, for the period 1 January, 2021–31 December, 2022. After consequent elimination of duplicates, of articles that were not English-written and "open access" and then applying PEDro classification/scoring-inspired, only 58 articles were selected for in-depth full qualitative reading. In the last stage,20 articles were "excluded with reasons", because they didn't offer significant information. Therefore, in our systematic literature review, 38 articles were included.**Results**: In the data gathered in this review we described the molecular pathways of activation of the immune system triggered by COVID-19, with significance on the clinical and paraclinical aspects of IMID patients infected with the new Coronavirus. Patients with IMIDs are at higher risk for hospitalization if diagnosed with SARS-CoV2 and more prone to severe outcomes and death. Risk factors associated with severe outcomes and death are: age, comorbidities, underlying disease activity, therapies used ("the good" being anti-tumor necrosis factor α, "the bad" – Methotrexate, Sulfasalazine, Azathioprine and "the ugly" – anti CD20 monoclonal antibodies). There were several reports of flares and new-onset of IMIDs after COVID-19 and after vaccination against this disease, but data from larger studies and registries do not confirm higher incidence of flare-ups or new-onset IMIDs. Regarding vaccination, of mounting importance is the timing between

immunomodulatory and immunosuppressive agents and the administration of the vaccine. And last but not the least, we discussed about Long COVID and the role of artificial intelligence in the pandemic and related-drug development. **Discussion and Conclusion**: The data in our systematic literature review is consistent with the expertise from our clinical practice. This article is the first part of the doctoral study that is centralized on the same topics, with the current objective of deepening the knowledge about the intersection of COVID-19/SARS-CoV2 and immune-mediated rheumatic diseases and a future objective: to compare information we have synthetized here with our database of almost 170 Romanian patients with a IMID and COVID-19/SARS-CoV2. The next objective is to extend the study to a multicenter control one.

Keywords: SARS-CoV2, COVID-19, Immune Mediated Rheumatic Diseases, Rheumatoid Arthritis, Systemic Lupus Erythematosus, COVID-19 Vaccine, Long COVID

1. Introduction

Motto:

"You may not control all the events that happen to you, but you can decide not to be reduced by them." — Maya Angelou

(As a hope, for the post-pandemic era): "Din bube, mucegaiuri și noroi/Iscat-am frumusețI și prețuri noi" - Testament, Tudor Arghezi

(COVID-19)/ (SARS-CoV-2) is a multisystem illness caused by a novel Coronavirus and brought a tremendous burden to the general population and the healthcare systems.[1]In many countries around the World, healthcare workers were profoundly outnumbered by the myriad of severe cases and the psychological burden in the setting of a little-known disease that killed many patients was high. As of 28th of May 2023, nearly 700 million of cases (infection and re-infection) and unfortunately approximately 7 million of fatalities worldwide were registered. [2]

Since its outbreak in Wuhan, China at the end of 2019, COVID-19 has transformed normalcy for the world. Given its unprecedented infectivity and pathogenicity, it was declared a global pandemic and tremendous efforts were made by the scientific community to understand the pathophysiology of the disease, aiming to develop effective preventive and therapeutic measures. [3]

It was initial thought that it is just a respiratory illness that affects the upper and lower airways, given the fact that many patients had mild flu-like symptoms. But that was not the case as further studies confirmed. COVID-19 is a multiorgan disease that can present with cough, high fever, anosmia, ageusia, intense fatigue, trouble breathing that can lead to acute respiratory distress syndrome (ARDS), neurologic and cardiovascular involvement that may result to multiple organs failure and eventually in death. Risk factors for mortality are: age, environmental factors such as smoking and comorbidities like diabetes, hypertension or lung and/or heart diseases. [4]

Strong evidence suggests that pathophysiological mechanisms of COVID-19 include immune dysregulation with impaired interferon and cytokine responses, endothelial activation and inflammation (endothelitis), as well as immunothrombosis, all leading to nucleotide-binding and oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome and nuclear factor kappa beta (NF-kB) activation leading, in some severe cases, to a cytokine storm with life-threatening manifestations. [3]

Our current armamentarium against Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) include general protective measures (mask covering face and mouth, frequent hand washing, distancing etc.), pharmacologic treatments (antivirals, convalescent

plasma, monoclonal antibodies and immunomodulators, anticoagulants etc.) and newly developed vaccines. [3]

Immune-mediated inflammatory diseases (IMIDs) comprise a clinically diverse group of systemic diseases having as common general feature the main pathologic symptomatic spectrum targeting the locomotor apparatus, with complex pathophysiological mechanisms and with no known cure. [5] The most important members of this class are rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjogren Syndrome (SS), systemic vasculitis (e.g.: Giant Cell Arteritis, Polymyalgia Rheumatica, anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitides – AAV), immune inflammatory myopathies (IIM) – Dermatomyositis (DM), Polymyositis (PM), Behcet's disease etc.

Such patients are some of the most vulnerable ones in the setting of infections, given the impaired immune system, COVID-19 not being the exception. They are believed to be at high risk for hospitalization, death related to SARS-CoV2 and their capacity to mount a good immune response to vaccines is decreased. Factors associated with the risk of severe outcomes are: disease activity, use of immunosuppressive medications (especially anti CD20 monoclonal antibodies) and comorbid conditions. [6]

More and more reports concerning COVID-19 associated autoimmune and rheumatic symptoms appeared as cases surged. These manifestations are noteworthy since they were associated with severe infection and increased morbidity.

To alleviate the burden of the disease, rapid development of vaccines was mandatory. Even though many pharmaceutical companies tried to manufacture the best vaccine against COVID-19, only few of them were FDA and EMA temporarily approved. Furthermore, for patients with IMIDs, the current recommendations are for mRNA vaccines. [7] One of the concerns about vaccination is its potential to cause autoimmune rheumatic complications, as well as flares of the underlying disease. [1]

2. Materials and methods

Given the extremely complex, difficult and encompassing aspects still under debate of the impact of SARS-CoV2 on patients with IMIDs, specifically RA, SLE, SSc, we have undertaken a comprehensive systematic literature review, based on the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) with the aim to help delineate the landscape of autoimmune rheumatic diseases in the setting of COVID-19.

The first step was to search for related articles in the period 1 January, 2021–31 December, 2022 interogating reputable international medical databases: National Center for Biotechnology Information (NCBI)/PubMed, NCBI/PubMed Central (PMC), Elsevier, Physiotherapy Evidence Database (PEDro), and —to verify whether the works found are published in ISI-indexed journals—the renowned ISI Web of Science database. [8,9] In searching, we used, contextually, specific keywords combinations/"syntaxes": "COVID-19", "SARS-CoV2", "Novel Coronavirus Disease", systemic lupus erythematosus", "SLE", "rheumatoid arthritis", "RA", "ankylosing spondylitis", "systemic sclerosis", "scleroderma", "SSc", "evolution", "antibodies ", "flare " (Table 1).

Keywords	Elsevier	PubMed	PMC	PEDro	Total
"COVID-19" + "systemic lupus erythematosus" + "evolution" + "antibodies " + "flare "	0	0	124	0	124
"COVID-19" + "SLE" + "evolution" + "antibodies " + "flare "	0	0	94	0	94

"SARS-CoV2" + "systemic lupus erythematosus" + "evolution" + "antibodies " + "flare "	0	0	38	0	38
"SARS-CoV2" + "SLE" + "evolution" + "antibodies " + "flare "	0	0	30	0	30
"Novel Coronavirus Disease" + "systemic lupus erythematosus" + "evolution" + "antibodies " + "flare "	0	0	7	0	7
"Novel Coronavirus Disease" + "SLE" + "evolution" + "antibodies " + "flare "	0	0	6	0	6
"COVID-19" + "rheumatoid arthritis" + "evolution" + "antibodies " + "flare "	0	0	170	0	170
"SARS-CoV2" + "rheumatoid arthritis" + "evolution" + "antibodies " + "flare "	0	0	51	0	51
"Novel Coronavirus Disease" + "rheumatoid arthritis" + "evolution" + "antibodies " + "flare "	0	0	16	0	16
"COVID-19" + "ankylosing spondylitis" + "evolution" + "antibodies " + "flare "	0	0	37	0	37
"SARS-CoV2" + "ankylosing spondylitis" + "evolution" + "antibodies " + "flare "	0	0	12	0	12
"Novel Coronavirus Disease" + "ankylosing spondylitis" + "evolution" + "antibodies " + "flare "	0	0	3	0	3
"COVID-19" + "systemic sclerosis" + "evolution" + "antibodies " + "flare "	0	0	46	0	46
"COVID-19" + "scleroderma" + "evolution" + "antibodies " + "flare "	0	0	32	0	32
"COVID-19" + "SSc" + "evolution" + "antibodies " + "flare "	0	0	28	0	28
"SARS-CoV2" + "systemic sclerosis" + "evolution" + "antibodies " + "flare "	0	0	15	0	15
"SARS-CoV2" + "scleroderma" + "evolution" + "antibodies " + "flare "	0	0	11	0	11
"SARS-CoV2" + "SSc" + "evolution" + "antibodies " + "flare "	0	0	14	0	14
"Novel Coronavirus Disease" + "systemic sclerosis" + "evolution" + "antibodies " + "flare "	0	0	4	0	4
"Novel Coronavirus Disease" + "scleroderma" + "evolution" + "antibodies " + "flare "	0	0	3	0	3
"Novel Coronavirus Disease" + "SSc" + "evolution" + "antibodies " + "flare "	0	0	4	0	4
Total	0	0	745	0	745

Table 1 - Sets of keywords/combinations of keywords/syntaxes used for the contextual searches and the related numerical results of our search

We selected only free/"open access" articles, English-written, and thus we firstly identified 745 articles. In the second stage/step, after removal of duplicates, there remained 212 articles that completed our list. For the third step, we checked for and retained only those issued in ISI-indexed publications – all 212 papers were eligible.

Further, in the fourth step, we indirectly evaluated the scientific impact/quality of each of the remaining articles, using a customized, quantification-weighted algorithm— PEDro classification/scoring-inspired. Articles that obtained a score of at least 4 ("fair quality = PEDro score 4–5") were further included. [10,11]After implementing this scoring, only 58 scientific papers qualified.

In the last stage/step of our literature research, we excluded 20 articles –"with reasons" - that did not qualify containing relevant and meaningful information regarding the approached topic and thereby 38 articles were selected as effective contributors to the bibliographic support of our work. " [see Fig.1 and Appendix]. To complete our work accordingly, we added some free-found in the literature additional bibliographic resources .

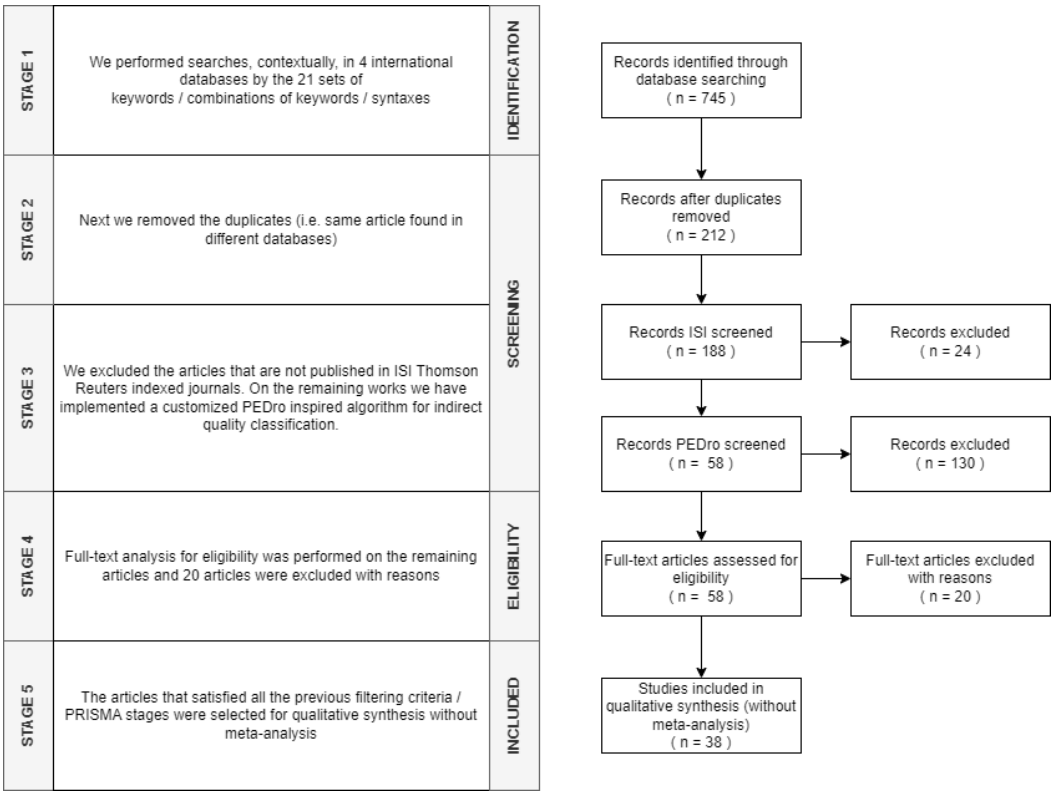

Fig 1 - PRSIMA DIAGRAM – customized to our systematic literature review

3. Results

In Table 2 there are presented the selected articles within our systematic literature review.

No.	Article	Publ. Year	No. of citations	No. of references	No. of citations/year	PEDro Score
1.	Acute and chronic neurological disorders in COVID-19: potential mechanisms of disease	2021	40	174	13,33	10
2.	Antibody-independent functions of B cells during viral infections	2021	14	98	4,67	5
3.	Anti-COVID-19 Vaccination in Patients with Autoimmune-Autoinflammatory	2021	13	122	4,33	5

	Disorders and Primary/Secondary Immunodeficiencies: The Position of the Task Force on Behalf of the Italian Immunological Societies					
4.	Autoimmune and Rheumatic Manifestations Associated With COVID-19 in Adults: An Updated Systematic Review	2021	32	169	10,67	10
5.	Common and Novel Markers for Measuring Inflammation and Oxidative Stress Ex Vivo in Research and Clinical Practice—Which to Use Regarding Disease Outcomes?	2021	23	479	7,67	9
6.	COVID-19: biologic and immunosuppressive therapy in gastroenterology and hepatology	2021	13	139	4,33	5
7.	COVID-19 Immunobiology: Lessons Learned, New Questions Arise	2021	16	250	5,33	6
8.	BNT162b2 vaccine-induced humoral and cellular responses against SARS-CoV-2 variants in systemic lupus erythematosus	2021	31	54	15,5	10
9.	Escape from X Chromosome Inactivation and the Female Predominance in Autoimmune Diseases	2021	26	55	8,67	10
10.	French recommendations for the management of systemic sclerosis	2021	14	94	4,67	5
11.	Immune-mediated inflammatory disease therapeutics: past, present and future	2021	32	61	10,67	10
12.	Impaired immunogenicity to COVID-19 vaccines in autoimmune systemic diseases. High prevalence of non-response in different patients' subgroups	2021	48	31	16	10
13.	Long COVID a New Derivative in the Chaos of SARS-CoV-2 Infection: The Emergent Pandemic?	2021	13	91	4,33	5
14.	Lymphopenia, Lymphopenia-Induced Proliferation, and Autoimmunity	2021	10	202	3,33	4

15.	Machine Learning Techniques for Personalized Medicine Approaches in Immune-Mediated Chronic Inflammatory Diseases: Applications and Challenges	2021	10	107	3,33	4
16.	Management of Rheumatoid Arthritis: An Overview	2021	65	240	21,67	10
17.	Potential Effects of Coronaviruses on the Liver: An Update	2021	13	280	4,33	5
18.	The cytokine storms of COVID-19, H1N1 influenza, CRS and MAS compared. Can one sized treatment fit all?	2021	29	405	9,67	10
19.	TLR9 and COVID-19: A Multidisciplinary Theory of a Multifaceted Therapeutic Target	2021	33	183	11	10
20.	Understanding and managing anti-MDA 5 dermatomyositis, including potential COVID-19 mimicry	2021	28	122	9,33	10
21.	A systematic review on mucocutaneous presentations after COVID-19 vaccination and expert recommendations about vaccination of important immune-mediated dermatologic disorders	2022	10	137	5	6
22.	American College of Rheumatology Guidance for COVID-19 Vaccination in Patients With Rheumatic and Musculoskeletal Diseases: Version 4	2022	17	100	8,5	10
23.	Coronavirus disease 2019 (Covid-19) vaccination recommendations in special populations and patients with existing comorbidities	2022	12	178	6	7
24.	Coronavirus Disease 2019 Outcomes Among Recipients of Anti-CD20 Monoclonal Antibodies for Immune-Mediated Diseases: A Comparative Cohort Study	2022	8	31	4	4
25.	COVID-19 in people with rheumatic diseases: risks, outcomes, treatment considerations	2022	44	137	22	10

26.	COVID-19 vaccine and autoimmunity. A new case of autoimmune hepatitis and review of the literature	2022	16	63	8	9
27.	Focus on Sex and Gender: What We Need to Know in the Management of Rheumatoid Arthritis	2022	9	105	4,5	5
28.	Hydroxychloroquine in systemic lupus erythematosus: overview of current knowledge	2022	8	244	4	4
29.	Immunogenicity of SARS-CoV-2 vaccination in rituximab-treated patients: Effect of timing and immunologic parameters	2022	7	26	3,5	4
30.	JAK inhibitors and COVID-19	2022	15	167	7,5	8
31.	Long COVID from rheumatology perspective — a narrative review	2022	10	73	5	6
32.	mRNA-based therapeutics: powerful and versatile tools to combat diseases	2022	23	564	11,5	10
33.	Multifunctional Role of S100 Protein Family in the Immune System: An Update	2022	12	164	6	7
34.	New Practical Aspects of Sweet Syndrome	2022	9	192	4,5	5
35.	Perspective on COVID-19 vaccination in patients with immune-mediated kidney diseases: consensus statements from the ERA-IWG and EUVAS	2022	10	87	5	6
36.	Pharmacological treatment of COVID-19: an opinion paper	2022	18	142	9	10
37.	Survival after COVID-19-associated organ failure among inpatients with systemic lupus erythematosus in France: a nationwide study	2022	9	22	4,5	5
38.	The Immunologic Profile of Vitamin D and Its Role in Different Immune-Mediated Diseases: An Expert Opinion	2022	7	174	3,5	4

Table 2. Table with authors, titles, journals and related links of selected articles in our systematic literature review

3.1. Antibodies and cytokine profile at the intersection of IMIDs and SARS-CoV2

SARS-CoV2 infection activates the immune response via multiple pathways. Extensive efforts have been made to decipher its mechanisms of invading the human body.

3.1.1. Molecular mechanisms of SARS-CoV2 infection that contribute to autoimmune symptoms

An exhaustive systematic literature review made by Tang and colleagues that included 187 studies following PRISMA algorithm, tried to summarize the potential molecular mechanism of COVID-19 that can contribute to rheumatic and autoimmune manifestations.

The most indisputable pathway by which microbial agents induce autoimmunity is by molecular mimicry – the structural similarity between microbial (foreign) and self-molecules, that can aberrantly activate the immune system at a further stimulation. [12] When analyzing peptide similarity, scientists reported massive hexapeptide and heptapeptide sharing between SARS-CoV2 spike glycoprotein and human proteins, including pulmonary surfactants, chaperons, brainstem neuronal proteins, ankyrin 1, heat shock proteins 60 and 90 etc. which contribute to organ manifestation related to autoimmunity. [1]

Another proposed mechanism is the characteristic of COVID-19 to trigger the production of autoantibodies. The presence of antinuclear antibodies (ANA) was observed in 4-50% of COVID-19 patients, but given the fact that most of them were older patients and such percentages of autoantibodies can be found in healthy older people, no conclusion can be drawn. (1,3) Nonetheless, there is a higher incidence of thrombotic and neurologic events in the group of patients with ANA positive testing. [1] Studies also have shown positivity for other autoantibodies like anti citrullinated protein antibody (ACPA), p-ANCA, c-ANCA, antinuclear ribonucleoprotein (anti-RNP), anti-centromere, Rheumatoid Factors (RF), antitopoisomerase I, anti-prothrombin, anti-cardiolipin, anti-beta 2 glycoprotein 1, but of no clear significance. [3,13] Additionally, there is a high positivity (10,2%) of anti-type I interferon (IFN) antibodies in patients with severe COVID-19, although there is no evidence of the presence of these antibodies before the infection.

The last pathogenic mechanism introduced in the aforementioned systematic literature review is the genesis of autoimmunity triggered by the magnified inflammatory reactions that ultimately lead to cytokine storm and organ damage, sometimes even to death. [1]

Multiple studies included in our review focused on the cytokine myriad in different stages of infection.

In the first line of defense are inflammatory cytokines: tumor necrosis factor α (TNF-α), interleukins (IL) like: IL-1β, IL-6, IL-8, IL-10, IFN-γ, chemokines: granulocyte colony stimulating factor (G-CSF), interferon gamma-induced protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein 1a (MIP-1a) [14,15]

3.1.2. Innate Immune Response Against SARS-CoV-2

The first line of defense is activated after the recognition of Damage-Associated Molecular Patterns (DAMPs) – released by the infected cells - and Pathogen-Associated Molecular Patterns (PAMPs) – virus-associated molecules - by Pattern Recognition Receptors (PRRs). Additionally, Toll-like Receptors bind their ligands and start to produce pro-inflammatory cytokines.

In the first hours post-infection, Type I and III IFN responses are activated, but coronaviruses evade the initial immune recognition and response via IFNs leading to high viral loads upon the onset of disease symptoms and a deregulated activation of the adaptive immunity, which in turn results in enhanced activation of the innate immunity as a compensatory mechanism. This can result in aggressive, uncontrolled inflammatory

response and the release of a large amount of pro-inflammatory cytokines and chemokines which cause damage in different organs/systems. [3]

Within the first two days post-infection, neutrophils are recruited first, followed by plasmacytoid Dendritic Cells (pDCs). From day 4, the immune response starts to switch to its adaptive arm, introducing as main actors monocytes and lymphocytes (T- and B-cells). [3]

One of the most studied pro-inflammatory cytokines is IL-6. A meta-analysis has demonstrated a nearly 3-fold higher serum levels of IL-6 in patients with complication of the SARS-CoV2 versus those with mild disease. [1,16] Other studies stated the fact that IL-6 is involved in the cytokine storm following infection [3,14]. It has an important role in vascular leakage and activation of the coagulation and complement cascade, which in severe cases may induce disseminated intravascular coagulation. [15]

It has been demonstrated that IL-6 induces lymphopenia and lymphopenia-induced proliferation in severe cases of COVID-19, maintaining the vicious circle [17]. Taking all into consideration, one thing is certain: IL-6 is linked to COVID-19 complications [16] and treatment with inhibitors of this cytokine has beneficial effects [14]. This molecule has a pivotal role in the pathogenesis and activity of some IMIDs like RA, SLE, SSc.

The endosomal receptors that belong to the family of Toll-like receptors (TLR) are of mounting importance in the antibody response. TLR 7 senses single-stranded RNAs like the one contained by SARS-CoV2. [14] Additionally, TLR 7 activation induces the secretion of type I IFN from pDCs and is considered the main reservoir of this pro-inflammatory cytokine. [3] TLR 7 is also associated with genetic susceptibility for rheumatic autoimmune diseases (RA, SLE, SSc).

In a study from 2021, Bezemar and Garssen proposed that TLR9 is closely linked to severe outcomes of COVID-19. TLR9 is broadly expressed on different cell types including epithelial ones in the lungs and nasal mucosa and its high concentration is observed in patients with ARDS, allergic asthma and rhinitis. Of all TLRs, TLR9 is most highly expressed on platelets contributing to their activation. Moreover, obese patients are associated with higher TLR expression on platelets. In vitro studies showed that TLR9 can shift the balance toward the procoagulant phenotype which is involved in early stasis, experimental venous thrombogenesis, neuroinflammation, muscle weakness, renal inflammation [18] It is well-known that the signaling pathway via TLR 9 has an important role for the pathogenesis of SLE. [14]

There cannot be an effective response of the immune system without complement activation that can lead to further inflammation and ultimately culminating to the destruction of the alveolar and epithelial cells through the generation of Membrane Attack Complex (C5b-C9), [3] the complement activation being one of the basics pathogenic mechanisms in most of the IMIDs. [19]

3.1.3. Adaptive Immune Response Against SARS-CoV-2

The second pillar of defense is centered by T lymphocytes (CD4+ T helper cells, CD8+ cytotoxic T cells, and T reg – regulatory T lymphocytes) and by B lymphocytes with the consecutive production of antibodies.

The specific chemotaxis of CD4+ T cells to the lungs may be partially responsible for lymphopenia in COVID-19 patients. In severe COVID-19, decreased numbers of CD4+ T-cells is detected, contributing to aberrant inflammation. [3] T reg were downregulated in COVID-19 patients, intensifying the immune response. [1]

3.1.4. Biochemical abnormalities

The biological markers that reveal systemic inflammation were also at higher concentrations (C reactive
protein, procalcitonin and ferritin). [1,17]

Lymphopenia is a marker used to predict COVID-19 severity, as it has been demonstrated that the lymphocyte number in the peripheral blood of COVID-19 patients gradually decreased as the disease progressed.
Lymphopenia affects primarily T (CD4+ and CD8+) and Natural Killer (NK) cells. It has been demonstrated that particularly the decrease in Th cells (CD4+) was marked in severe cases. [17]. This generates lymphopenia induced proliferation that force the immune system to secrete more lymphocytes maintaining chronic inflammation. [20]
Interestingly, a novel marker for predicting the severity of COVID-19 has emerged - the increased neutrophils/lymphocytes ratio. [3,15]
Lymphopenia (and consequently lymphopenia-induced proliferation) is a marker of clinical activity of RA, SLE, SSc and Sjogren Syndrome [17] thus the observation that patients with active IMIDs can suffer devastating consequences after SARS-CoV2 infection, the vicious cycle of lymphopenia being maintained.
One of the most characteristic features of COVID-19 is the hyperactivation of the coagulant cascade and a relatively exhausted anticoagulant and fibrinolytic system with increased levels of D-Dimers and consequent formation of microthrombi in small and large vessels. [15]
Another interesting and not well-known marker proposed for predicting severe cases of COVID-19 is the activity of S100 family proteins that play important roles in the immune system and IMIDs as alarmins (DAMPs), antimicrobial peptides, pro-inflammation stimulators and chemo-attractants during an innate immune response. Singh and colleagues made a thorough literature review and offer insights on the involvement of S100 protein members in abnormal immune activation during the pathogenesis of SARS-CoV2 infection. [21]

3.2. Is gender important?

It is well studied and well-known from our clinical practice that immune mediated inflammatory diseases like rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis impact women and men differently.
Women have a faster and better-quality immune response than men of the same age and of a higher amplitude to different pathogens and vaccines [22,23]. When it comes to infections, women's defense mechanisms are very rapidly and strongly activated – they develop a more robust cytokine response resulting in a higher level of CD4+ T helper cells and also B cells, thus higher level of circulating antibodies than men [22]. Yet, the above mentioned IMIDs are obviously more frequent in women (see below). [24]
Rheumatoid arthritis is a chronic, systemic immune mediated inflammatory disease where one can see clearly the women predominance. Maranini and colleagues analyzed the latest and most important literature data addressing gender discrepancies in patients with RA. They observed that women tend to have a higher blood drug concentration and longer specific – disease-modifying antirheumatic drugs (DMARDs) drug clearance times, making them more prone to adverse reactions, rising the concern that dosing should be different in females than in males. [23]
The undisputable cause for the female bias regarding autoimmune diseases is the sex hormone, estrogen, that downregulates inflammation pathways and upregulates antibody production [23]. The most potent form of estrogen, 17β estradiol, enhances the in vitro production of IFNα in pDCs that were exposed to Toll-like Receptor 7 (TLR 7) stimulation. Moreover, it has a conflicting effect based on its concentration – at lower titers it increases the production of pro-inflammatory cytokines: IL-1, IL-6, TNFα and at higher concentration it decreases the level of the aforementioned molecules. [23]
Nonetheless, in a recent paper published, Youness and colleagues, the role of the sex chromosome, more specifically the escape from X-chromosome inactivation (XCI) as a possible mechanism for the female predominance in immune mediated diseases, has emerged.

The X-chromosome is bigger than the Y-chromosome and encodes more than 1000 genes, many of which are involved in immune response (WAS, BTK, FOXP3, IL2RG etc.). To ensure the fact that X-chromosomal genes are not expressed at twice the levels of expression in males (XY), early in embryonic development of females, one of the two X-chromosomes is randomly and permanently inactivated. This process is called X-chromosome inactivation or lyonization. Certain genes (15-23%) can escape XCI, including TLR 7, CXorf21, CYBB, KDM6a, CXCR3, BTK, IL13RA1, CD40LG, IRAK1. From this myriad of genes, of most importance for our literature review also is the endosomal Toll-like Receptor 7 (TLR 7), located on the short arm of the X-chromosome, expressed primarily in pDC, B lymphocytes and monocytes. Its key role in infections (including SARS-Cov2 infection) is well established. After viral infection, activation of TLR7 in monocytes preferentially promoted the expression of CD4+ T helper 17 (Th17) lymphocytes thus triggering pro-inflammatory cytokine response. In young men with COVID-19, mutations of TLR 7 genes were associated with severe forms of the disease. [22]

Studies from seasonal influenza vaccine efficacy on patients with RA reveal that women show more robust immune response with higher concentration of antibodies than men and B cells from female mice were associated with higher expression of TLR7. From the reports of the COVID-19 vaccine companies, women were more prone to anaphylaxis and thrombotic events. [23]
Regarding autoimmunity, TLR7 is of mounting importance in the B lymphocytes response in SLE, the production of anti-ribonucleoprotein (RNP) autoantibodies and type I IFN (IFN-I) by pDCs.

3.3. Clinical and biological impact of SARS-CoV2 infection in patients with IMIDs

Immune mediated rheumatic diseases are systemic diseases that dampen the immunity of the patient. It is intuitively thought that any infection (including COVID-19) has an additional negative impact, worse prognosis and higher risk of complications in this group of patients than in the general population.

3.3.1. Rheumatic manifestations in the spectrum of autoimmunity in patients with COVID-19

Tang et al reviewed studies focusing on the clinical autoimmune and rheumatic manifestations associated with the coronavirus disease 2019 and the potential molecular mechanisms contributing to these manifestations. All these symptoms are important because of the challenge they bring to the differential diagnosis of a new-onset rheumatic disease/a flare of a pre-existing IMID or simply symptoms of infection.
Articular involvement ranges from arthralgia, acute arthritis (mono-/oligo-/polyarthritis) to chronic arthritis (one case report described a rheumatoid arthritis flare). [1]
Myalgia and muscle weaknesses resembling an immune-mediated inflammatory myopathy-like (IMIM-like) disease is also very common. But what is strikingly found from the literature research we performed is the similarity between severe COVID-19 and anti-melanoma differentiation-associated gene 5 Dermatomyositis (MDA5-DM): a type of IMIM recently described. MDA-5 is a Retinoic Acid Inducible Gene-1 (RIG-1)-like receptor that is coded by interferon-induced helicase C domain-containing protein 1 (IFIH1) gene that recognizes double stranded (ds) RNA of viruses and induces a type I interferon response. After the viral replication and cell lysis, MDA5 or a viral-MDA5 complex is released, resulting in autoantibody production against it, thus perpetuating cell injury, exposure of self-antigens and consequently maladaptive immune response resulting in disease. Both diseases have a similar involvement of the lung, skin rashes, fever, fatigue and myalgia, similar blood cytokine profiles with elevated biologic inflammatory

syndrome (elevated ferritin and C-reactive protein levels), the same invasion and destruction mechanism (endothelial dysfunction, vasculopathy, autoantibodies attack) . Furthermore, the radiologic imagery of SARS-CoV2 pneumonia is comparable to the interstitial lung disease (ILD) in anti-MDA5 DM, with frequent presence of diffuse ground glass opacities suggestive of peribronchovascular consolidations. Severe COVID-19 and anti-MDA5 DM share the same treatment – except for anticoagulants - with high-dose steroids, immunosuppressants and anti-cytokine therapy.

During the pandemic, there was a high flare and hospital admission rate among patients with myositis advocating for a role of latent viral infection and molecular mimicry in the pathogenesis of anti-MDA5 DM. [25]

Skin manifestations include Raynaud's phenomenon, chilblains-like lesions, cutaneous vasculitis (purpuric papules and plaques, urticarial lesions, hemorrhagic bullae), livedo reticularis and psoriasis. Systemic vasculitis with lung, kidney, brain, ileocecal, splenic, retinal involvements, was also present in case reports, with negative outcomes. [1]

Hematological features encompass thrombocytopenia with autoimmune thrombotic thrombocytopenic

purpura and autoimmune hemolytic anemia.

The majority of SARS-CoV2 infected patients have lung involvement manifested by trouble breathing (that can be so severe that mandates orotracheal intubation) and imagistically can range from interstitial mononuclear inflammatory infiltrates, organizing pneumonia, pleurisy, ground-glass opacities or fibrosis on the long term, with accompanying respiratory dysfunction on respiratory tests (spirometry, DLCO). [1,25]

SARS-CoV2 is associated with acute and chronic involvement of the nervous system. Of major interest for patients with rheumatic diseases are cerebrovascular diseases associated with COVID-19 – stroke (that include both arterial and venous thromboembolic events), cerebral venous sinus thrombosis – especially in patients with antiphospholipid syndrome (APS). There is evidence in the literature of positivity of one or more of autoantibodies related to APS during SARS-CoV2 infection in patients that were "free" from this diagnosis and from other thromboembolic events and also a higher titer of autoantibodies in patients with APS. [26] The presence of these autoantibodies is a marker for COVID-19 severity, although some results could have been false positive due to prior anticoagulation therapy. [1] Nonetheless, the need for anticoagulation cannot be questioned in those cases. Additionally, IMIDs are characterized by endothelial disfunction and thus it is reasonable to believe that this category of patients can have a poor prognosis when infection with SARS-CoV2 occur.

Another diagnostic challenge are the peripheral neuropathies and myalgia and muscle weaknesses that may occur naturally in the evolution of rheumatic diseases or be the first clinical presentation of an IMID versus the ones associated with COVID-19 (Guillain-Barre, Miller-Fisher syndromes). Electromyographic studies, autoantibodies and muscle biopsy can clarify the correct etiology. [26]

3.3.2. General aspects on evolution of Coronavirus Disease 2019 in patients with IMIDs

Given the vulnerability of the immune system of an individual with an IMIDs and after extensive studies in the literature, it is concluded by now that this category of patients is at an increased risk for hospitalization, and potentially of severe outcomes consequent to COVID-19, taking into account some of the risk is attributable to comorbidities.

Grainger et. al offered in a paper from 2022 insights of the "COVID-19 Global Rheumatology Alliance (C19-GRA) physician-reported registry of people with rheumatic diseases and COVID-19" that was launched at the beginning of the pandemic and has >20,000 records from individuals and their detailed demographic and clinical data about the IMIDs, its treatments and the COVID-19 disease course, from 81 countries. In the first months of the data collection (until June 2020) the observation that the risk of death was associated with age, comorbidity and glucocorticoid use (≥10 mg prednisone-equivalent

daily) was made. Furthermore, disease activity at the time of COVID-19 diagnosis, therapy with Rituximab (RTX) and Sulfasalazine (SSZ) were other rheumatic-disease risk factors for death.

Another interesting fact that came up from another analysis up to august 2020 is that ethnicity is also important. White patients were at lower risk for requiring ventilatory support and of hospitalization for COVID-19 than African American, Latin and Asian patients. [27]

3.3.3. Specific rheumatic diseases and COVID-19 impact

Andrei-Flavius Radu and Simona Gabriela Bungau, two Romanian authors, made a comprehensive literature review that satisfied the PRISMA methodology about the management of RA; in this review, the authors concluded the evolution of RA patients infected with SARS-CoV2 is similar to general population, according to data from cross-sectional and cohort studies published so far, although it appears that serum ACPAs levels rise in the course of infection. [28]

Mageau et al. performed a cohort study on systemic lupus erythematosus patients with COVID-19 associated organ failure (AOF) that were registered in the French national medical/administrative hospital database from January 2011–November 2020 period. Each patient was randomly matched with five non-SLE patients with COVID-19-AOF. They matched 190 patients with SLE and COVID-19-AOF and 908 non-SLE COVID-19-AOF. After 30 days of hospitalization 22,6% deaths occurred in the first group of patients versus 21,8% in non-SLE patients with COVID-19-AOF: HR 0.98 (0.71–1.34).

From the patients that could have a follow up in the next 30 to 90 days (75 in the first group and 299 in the second one), the authors observed that 25,3% of patients in the first group versus 15,4% in the second group deceased, concluding that "COVID-19-AOF is associated with a poor late-onset prognosis among patients with SLE." [29]

3.4. New-onset and flares of IMIDs after SARS-CoV2 infection and vaccination

There are reports in the literature with reference to new-onset IMIDs – three cases of SLE (two of them eventually deceased), myositis, but also to flares of SLE (the most reported rheumatic disease flare up), ankylosing spondylitis, psoriatic arthritis, polymyalgia rheumatica (one patient). [1]

3.5. Disease-modifying antirheumatic drugs (DMARDs) and COVID-19

3.5.1. Which DMARD is better and which is worse in the setting of COVID-19? ("The good, the bad and the ugly")

Concerning the therapy used for the IMIDs: targeted synthetic DMARDs (tsDMARDs) and biological DMARDs (bDMARDs), to all appearances, "the good" is antiTNFα therapy: it offers better outcomes for patients with COVID-19 than Janus kinase (JAK) inhibitor, rituximab (RTX), azathioprine (AZA) or 6- mercaptopurine monotherapy, methotrexate (MTX) monotherapy. Overall, the data from this registry suggests that the use of many conventional synthetic DMARDs and bDMARDs does not confer increased risk of poor outcomes in COVID-19, the most notable exception being the use of RTX and the challenge in this situation is to properly balance the severity of the IMID and the risk of COVID-19 harsh evolution. [27]

From a study that focuses mainly on Coronavirus impact in gastroenterology and hepatology, we discovered another study with more than 2,000 patients with IMIDs (psoriasis, RA, spondyloarthritis and inflammatory bowel diseases). The verdict was that cytokine inhibitors at least partially protect against severe SARS-CoV-2, given the fact that fewer patients with IMIDs receiving cytokine blocker therapy (exception for the B cells depleting therapy) had SARS- CoV-2 IgG seroconversion than patients without such therapy and healthy individuals. [4]

According to our clinical practice and from the myriad of studies and registries data, "the bad" appears to be MTX, SSZ and AZA and "the ugly" seems to be B cell depleting therapies, namely Rituximab and in small number of cases Ocrelizumab. These monoclonal antibodies eliminate circulating pre-B cells and B mature cells, resulting in an impaired immune response to infection by decreasing the antibody production. [6,27]
A comparative cohort study was conducted by Patel and colleagues and included 114 patients that received B cell depleting therapy within one year prior to COVID-19 diagnosis in the time period of 31st of January 2020 and 31st of January 2021, matched up 5:1 by sex, age and COVID-19 PCR date. They adjusted the hazard ratio (for age, race, body mass index, and Charlson Comorbidity Index) and used 95% confidence intervals (CIs) for hospitalization, mechanical ventilation, and death. They concluded that patients in the first group (treated with B cell depleting therapy within one year prior to COVID-19 diagnosis) had higher mortality following COVID-19, but risk of hospitalization and mechanical ventilation use was similar to matched comparators. [6]
New American College of Rheumatology (ACR) guidelines recommend that patients with RMDs that are at high risk for poor outcomes related to COVID-19 should receive monoclonal antibody therapy either as prevention or as treatment for newly symptomatic patients. [7]

3.5.2. Anti-rheumatic drugs used as potential treatment for COVID-19 in non-rheumatic patients

A) Hydroxychloroquine (HCQ)

Hydroxychloroquine (HCQ) is an immunomodulator, well-tolerated antimalarial drug that is used in IMIDs (having a major role in systemic lupus erythematosus), infectious, metabolic and neoplastic disorders. Its mechanism of action is complex and still under debate. It has a high lipophilicity, lysosomotropism and pH and can penetrate cell membranes and accumulate into lysosomes where it interferes with key cellular functions via the inhibition of the TLRs and of the Cyclic GMP-AMP synthase–Stimulator of Interferon Genes (cGASSTING) pathway. This results in inhibition of enzyme and cytokine release, receptor recycling, plasma membrane repair, cell signaling, apoptosis and autophagy of the cells, inhibition of the NK cells, and overall disrupts energy metabolism. [30,31]
Considering the pathogenic mechanisms we described in section 3.1., there is sufficient evidence to understand the rationale behind using this drug in SARS-CoV2 infected patients.
However, recent studies demonstrated no added benefit for using HCQ in hospitalized patients. [31]

B) Tocilizumab (TCZ)

As aforementioned, IL-6 is one of the main cytokines that is present in high concentration during the acute phase of COVID-19 and intuitively drugs that block this molecule or its receptor should be used as a treatment. One of these medications is Tocilizumab, used for the treatment of RA and is a monoclonal antibody against IL-6 receptors. There are studies from the beginning of the pandemic that support the idea that adding TCZ in the treatment of severe COVID-19 cases increased the oxygenation efficacy to 5% and the hospital discharge rate to 95%. Concerning the side effects, it can cause transient drug-induced liver injury and pancytopenia. "Tocilizumab should be stopped when the serum neutrophil is lower than 1,000 cells/mm2, platelet is lower than 100,000 cells/mm, and/or hepatic enzymes are higher than three times of the upper normal limit." [32]
On the contrary, the registry clinical trials (COVACTA, EMPACTA) failed to show benefit in patients with severe pneumonia, including patients requiring ICU admission or mechanical ventilation. [31] But the most important study that added to its approval of use in COVID-19 patients was the RECOVERY study that concluded that TCZ was effective in

reducing mortality in patients with systemic inflammation (CRP >75 mg/L in this study). [31]

C) Baricitinib

A thought-provoking inflammation pathway is Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway that in SARS-CoV2 infection is involved in complement hyperactivation of respiratory epithelial cells, in the activation of CD4+ and CD8+ T lymphocytes, NK cells and monocytes. These trigger high concentration of pro-inflammatory cytokines, promotes senescence of SARS-CoV2 infected cells, which heighten inflammation. [33]

A novel pathogenic treatment for some IMIDs (especially RA) is with small molecules – targeted synthetic DMARDs. An important member of this class is Baricitinib, a JAK-STAT pathway inhibitor, particularly of JAK1 and 2, approved for the treatment of RA, alopecia areata and COVID-19, especially in the hyper- response phase of the infection. However, the risk of other co-infections and cardiovascular toxicity, in particular thromboembolic events, should be taken into consideration. [5,32] There are also reports in the literature of adverse hepatic effects, particularly cholestasis and hepatitis. [32]

Besides its anti-inflammatory effects, some experimental evidence establishes that Baricitinib has also antiviral potency. Furthermore, there is a report in the literature of a series of patients with bilateral COVID-19 pneumonia treated with Baricitinib. The patients had clinical and radiologic recovery, a rapid decline in SARS-CoV-2 viral load, inflammatory markers and IL6 levels. In another retrospective multicenter study (NCT04358614) on patients with COVID-19 moderate pneumonia, the result was that baricitinib reduced COVID-19 mortality rate, intensive care unit admissions and SARS-CoV-2 viral burden in nasopharyngeal swabs and when used during 14 days did not induce adverse effects. Nonetheless, it is not recommended for patients requiring mechanical ventilation or (Extracorporeal membrane oxygenation)ECMO, given the lack of data in the literature.

However, Tofacitinib and Ruxoltinib, other 2 JAK-STAT inhibitors were not approved by WHO in the treatment of patients with COVID-19 regardless of the severity of the disease, and the benefits outweighs the risks. [33]

D) Anakinra

Last but not the least, an IL-1 inhibitor, Anakinra, that is approved in the treatment of Rheumatoid Arthritis, Gout and autoinflammatory syndromes like Cryopyrin-Associated Periodic Syndrome (CAPS), familial Mediterranean fever and also Still's disease, and Deficiency of Interleukin-1 Receptor Antagonist, was studied in the setting of COVID-19. It has shown beneficial effects on clinical progression and mortality in patients with severe pneumonia. [31]

Soluble urokinase plasminogen activator receptor (suPAR) is used as a biomarker for the level of activity of the immune system in response to an inflammatory stimulus and positively correlates with pro-inflammatory biomarkers. [34] In a double-blind clinical trial, Anakinra displayed increased benefit especially in patients who had elevated suPAR levels (>6 ng/mL), a marker of severity in patients with COVID-19 [31].

E) **Vitamin D**

It is well-accepted that vitamin D supplementation is associated with lower risk of acute respiratory infections, such as influenza. [31] Given the fact that it has an important role in innate immunity including but not limited to Toll-like Receptor activation and lowering inflammatory neutrophil-derived cytokine production, but also in adaptive immunity regulating the production of T lymphocytes and inhibiting IFNγ production, Vitamin D supplementation in acute phase of COVID-19 could be effective. [35]

One of the first studies that support this affirmation was a pilot randomized controlled trial in Spain, where experts agreed that high-dose calcifediol reduces the need for intensive care unit treatment in patients hospitalized for COVID-19. [31]

The in-depth pathogenic role of Vitamin D in the immunity referring to the IMIDs will be the subject of a different article of ours.

3.6. Long COVID patients – "the great forgotten"

Long COVID (LC) is defined as the persistence of multi-organ symptoms after COVID-19 that prevail 4 weeks after initial infection and there is no other explanation for an alternative underlying disease.

A systematic literature review conducted by Fernandez-Lazaro and colleagues offered a comprehensive image about the pathophysiological changes and clinical characteristics of patients that suffer from LC syndrome. Firstly, the persistence of the active virus located in tissue reservoirs or cells of the immune system lead to altered immune response characterized mainly by an increase in IFNγ and IL-2, IL-6, IL-10 cytokines, pathological decrease in populations of CD4+, CD8+ lymphocyte subpopulations that can lead to lymphopenia induced proliferation, deficits of B lymphocytes and monocytes (that induce the renewal and generation of this lymphocytes that may cause further inflammation), alterations in the cellular response to SARS-CoV-2 antigens and decreased levels of the Chemokine ligands 4 (CCL4). Moreover, in the setting of the cytokine storm with consequent multisystem inflammatory syndrome (MIS), the persistent high concentration of pro-inflammatory markers can induce LC.

Secondly, the formation and persistence of autoantibodies (against IFN, neutrophils, anti-nuclear and cyclic citrullinated peptides) that was observed in some studies in up to 50% of patients with severe COVID-19, impair virological control by inhibiting immunoreceptor signaling and altering the composition of peripheral immune cells.

Additionally, the authors proposed thyroid dysfunction (that would cause autoreactive T cells to escape negative selection in the thymus and contribute to tissue injury), dysbiosis and nutritional deficiencies (omega-3 fatty acids, vitamin C, vitamin D, Zinc and Selenium) as further pathogenic mechanism for LC. [20]

3.6.1. Why is Long COVID important for rheumatologists?

Given the heterogeneity of symptoms related to an apparently systemic disease, the differential diagnostic between Long COVID in a patient with an IMID or a flare-up of the pre-existing disease, is very difficult.

Arthralgia/inflammatory arthritis – the most common manifestation that bring the patient to the rheumatologist - can also be encountered in LC syndrome. Regarding the potential causality of SARS-CoV2 to trigger new onset RA, there is conflicting evidence in the literature: some authors suggest that the new onset of RA post-COVID-19 could be coincidence rather than causality and some authors propose COVID-19 as a trigger for RA. [26,36]

Myalgia is also a common and non-specific symptom that can be found in patients with Long COVID and an IMID. If the latter is the case, the patient conjointly has other symptoms such as Raynaud's phenomenon, skin rashes (e.g., malar rash, Gottron's papules) and evidence of strongly positive autoantibodies in the blood.

One of the most prevailing and bothersome symptoms of patients with LC is breathlessness, frequently present also in patients with IMIDs. The difficulty in distinguishing between a new-onset IMID with pulmonary involvement and LC comes from the fact that both groups of diseases can elicit pulmonary fibrosis-like lesions on imaging studies.

Regarding the laboratory markers, there are some clues that can shed a light on a diagnosis of a IMID rather than LC: persistence of antibodies, pancytopenia (although lymphopenia is frequent in LC patients), high concentration of inflammatory biomarkers (erythrocyte sedimentation rate - ESR, CRP, ferritin). [36]

There are also a variety of other signs and symptoms like dermatological (pernio lesions, livedo reticularis), fatigue, back pain, sicca syndrome, headaches, mononeuritis etc. that

together with biologic inflammatory syndrome, pancytopenia, coagulopathies, pulmonary fibrosis on imaging studies and in some patients persistence of autoantibodies, that can make the differential diagnosis between a patient with Long COVID and a new-onset IMID very troublesome and clinicians have to keep in mind the whole clinical and paraclinical image of the patient.

3.7. Vaccination against SARS-CoV2

3.7.1. General aspects

Given the fact that the world was challenged by a relatively new pathogen – SARS-CoV2 but in the same time the medical teams had sufficient data about the Coronaviridae family, from which SARS-CoV2 belongs to, the need for an unprecedented global effort for the developing a vaccine that could ease the burden of the pandemic, emerged.
The rationale behind the rapid development of vaccines against SARS-CoV2 was to interrupt viral spread and thus limit pandemic duration or hopefully crumble it. [37]

3.7.2. Vaccination for patients with IMIDs

3.7.2.1. General aspects and evidence data

Patients with IMIDs are a category of individuals supplementary vulnerable if they become infected with SARS-CoV2, because of the impaired immune response as a disease consequence. Additionally, they are at high risk of any type of infection, including COVID-19. Thus, they are a part of a category of patients that is prioritized for vaccination against SARS-CoV2, even though they may show impaired immunogenicity to vaccines. [7,38–40]
The latest ACR recommendations from May 2022 state as an overarching principle that the rheumatologist is responsible for engaging the patient in a discussion and in a shared decision-making process about vaccination. [7]
For patients with IMIDs the current recommendation is for immunization with mRNA vaccines over the disabled adenovirus vaccine, for which wider scientific knowledge and clinical experience are available. [7,37]
Booster doses are recommended to be made more than 28 days after the last vaccine dose in patients with IMIDs receiving any immunosuppressive or immunomodulatory therapy other than HCQ. [7]
A very extensive study conducted by Ferri et al. aimed to assess the seroconversion after the vaccination cycle and at 6-12-month follow-up, as well the safety and efficacy of vaccines in preventing COVID-19 in patients with IMIDs from all across Italy. They included 478 patients (mean age 59 ± 15 years), namely 101 RA, 38 SLE, 265 SSc, 61 cryoglobulinemic vasculitis (CV), and a miscellanea of 13 systemic vasculitis matched with 502 individuals from the general population (mean age 59 ± 14 years). They measured serum IgG-neutralizing antibody (NAb) on samples obtained within 3 weeks after vaccination cycle. The results were as expected: in patients with IMIDs there were significantly lower NAb levels and higher percentage of non-responders to vaccine compared to controls. When assessing the subgroups, the authors revealed that patients with interstitial lung disease and those treated with glucocorticoids, Mycophenolate-Mofetil (MMF) or RTX were at higher risk of non-response to vaccine. Regarding the adverse effects after vaccination, there was no significant difference between the two major groups. Of note, the majority of patients experiencing flares had CV (60%). [41]

3.7.2.2. Recommendations for the timing of DMARDs administration and anti-SARS-CoV2 vaccination

From the literature review conducted by Seirafianpour et al that gathered vaccine recommendations for IMIDs patients, we noted like, as in other guidelines, vaccination in this category of patients should be made when the disease is stable or in low-activity stage, before starting a new immunosuppressive agent. High risk patients that are mainly advised for vaccination are SLE patients receiving “cytotoxic therapy “ and higher-dose

glucocorticoids and the ones treated with RTX therapy regardless of the pre-existing disease.

In regards to corticosteroids and vaccination, one study recommends that patients on monthly intravenous pulse of Cyclophosphamide and Methyl prednisolone therapy should vaccinate either prior to therapeutic scheme or one month after the completion of 6 months pulse therapy. Another recommendation is to decrease Prednisone dosage to less than 10mg daily for 10 days before and after each dose of the vaccine. [38,39]

Patients should withhold MTX and JAK inhibitors one-two weeks after each vaccine dose for patients with controlled disease. [27,38,39]

Patients should postpone subcutaneous Abatacept (ABA) both one week prior and one week after the first dose of vaccine. [7,38]. Regarding ABA infusion, patient should schedule it 4 weeks before the first dose of the vaccine and postpone the next i.v. with a week after the vaccination, and no adjustment is needed for the second dose of vaccine. [38] However, ACR recommends that vaccination should be made 1 week prior the next doze of i.v. Abatacept. [14]

RTX should be delayed 2-4 weeks after the second vaccine dose if the activity of the disease allows. Furthermore, other study suggests that while on RTX therapy, patients should receive their vaccine either one month prior the initiation of RTX or 6-8 months after the infusion. [7,38,39]

Rituximab has raised the avidity of further studies. Magliulo et. al conducted a prospective single center study with 41 fully vaccinated and able to obtain anti-spike antibodies serologies. The patients received SARS-CoV-2 vaccines 24 weeks post-RTX infusion for an established IMID. Seroconversion measured by anti-spike antibody serologies was seen in 36,5% of patients, with no significant difference in seropositivity rates amongst the different vaccine types (BNT162b2 mRNA, mRNA-1273, Ad26.COV2.SCovid-19). The seropositive group was of younger age and had a longer average interval between vaccine doses. The underlying IMIDs and concomitant medications in addition to RTX had no effect on the seroconversion rates. Hypogammaglobulinemia (IgG and/or IgM), B cell numbers, or concomitant immune suppressive medications were correlated with sero-negativity ($p = 0.004$). [42]

Regarding Tocilizumab, some studies have reported there should be at least 12 weeks between its administration and vaccination to have the ideal antibody response while other studies with non-COVID vaccines showed that TCZ therapy does not impair their immunogenicity.

Belimumab should be delayed for 1-2 weeks (if disease activity allows) after each vaccine dose. [7]

One single article from our systematic literature review that collected data from the C19-GRA registry revealed that patients with IMIDs treated with MMF are associated with substantial impairment of humoral immunity following SARS- CoV-2 vaccination, given the fact that MMF inhibits inosine monophosphate dehydrogenase, which impairs proliferation of lymphocytes and cell-mediated and humoral immune responses. [27]

Some studies suggest that household contacts of a patients with an IMIDs should also be vaccinated, to facilitate a "cocooning effect" that may further protect the patient. [7,38]

ACR also recommends that ideally, vaccination should be made in patients with well-controlled disease, but in the same time it should occur as soon as possible for those for whom is being recommended (high risk patients) regardless of the disease activity status. If the patient has a life-threatening complication of the pre-existing disease that requires ICU treatment, vaccination should be deferred. [7]

The Italian Task Force on Behalf of the Italian Immunological Societies issued recommendations in 2021 for Italian patients with IMIDs. They are generally the same as other studies have shown, inactivated vaccines or vaccines containing non-infectious viral sequences may be safely administered but no modification of immunosuppressive therapy either during or following vaccination is advisable, because of a possible flare up after the

interruption of immunosuppressive drug. There are some exceptions from this latter rule – corticosteroids should be used in lower doses than 10 mg daily prednisone-equivalent and anti CD20 monoclonal antibodies should be interrupted (according to ACR updated recommendation). Moreover, the immunologist will evaluate if therapy with MTX, ABA and JAK inhibitors should be discontinued or not. [37]

3.7.2.3. IMIDs and impaired vaccine response

Among IMIDs, systemic lupus erythematosus patients could have an impaired vaccination response because of the pathogenic down-regulation of the IFN 1 axis by the disease itself and impaired lymphocyte functions. [43]

Moyon et. al conducted a prospective study that included 126 patients with SLE that were vaccinated with BNT162b2 mRNA vaccine. They evaluated disease activity and clinical assessments from the first dose of vaccine until day 15 after the second dose. Based on their analysis, they concluded that BNT162b2 was well tolerated and no statistically significant variations of disease activity scores [BILAG (British Isles Lupus Assessment Group) and SLEDAI (SLE Disease Activity Index)] were observed regardless of the active and inactive disease at baseline. There were two immunosuppressive agents that severely reduced antibody response - MMF and MTX . Anti-spike antibody response was positively associated with baseline total immunoglobulin G serum levels, naïve B cell frequencies and SARS-CoV2-specific T cell response [measured by a whole blood Interferon-Gamma Release Assay (IGRA)]. [43]

Data from SSc patients and vaccination are scarce. French authors recommendations state that patients with SSc should be administered to all patients with confirmed ILD the annual anti-flu vaccination and the anti-pneumococcal vaccination. The anti-COVID-19 vaccine follows the same recommendations as for patients with other IMIDs. [44]

3.7.2.4. Safety issues

The issue of a flare up of the pre-existing IMID should be considered because of vaccine stimulation, as well as possible new-onset of such a disease, but the benefit of vaccination outweighs the potential risk. There is an impaired vaccine response in patients with IMIDs receiving systemic immunomodulatory therapies. [7,37,39]

mRNA vaccines seem to be well tolerated in patients with IMIDs with low percentage of flare ups and with the same frequency of adverse effects as in the general population. [38,39]

Seirafianpour et al. made a systematic literature review that gathered 180 articles on mucocutaneous presentations and autoinflammatory disease flare ups (but not exclusive to IMIDs) after COVID-19 vaccination. They concluded that a total of 13 patients with IMIDs had flare ups of their disease, including known cases of Behcet's disease (31%), SLE (15.33%) and other (DM, arthritis) (15.33%).

From the SLE flare-up category, the authors described the case of a 78-year-old woman with that presented with fever, arthritis, erythematous rash (generalized acute cutaneous lupus), purpura and oral aphthous ulcers after 2 days of inoculation with the 1st dose of BNT162b2; biopsy from purpura showed leukocytoclastic vasculitis and consequently treatment was done with hydroxychloroquine; other case of a 50-year-old woman received the 1st dose of ChAdOx1S nCoV-19 and presented with severe hemolysis and arthralgia in addition to oral and nasal ulceration 14 days post-vaccination. Eventually, she was treated with oral corticosteroid and rituximab (?-o.n.). [38]

Data from C19 Registry showed an increase percentage of self-reported flare rates among 1,101 patients with rheumatic diseases (not exclusively IMIDs) who received mRNA-based vaccines (17%), with 23% of the flares occurring only after the first dose, 43% only after the second dose and 33% after both doses. Factors associated with these flares included prior COVID-19 or previous flare (within 6 months of vaccination) and use of combination immunomodulatory therapy. However, four other studies that included more than 6000 patients with an IMIDs that received a mRNA vaccine reported no notable flares of the underlying disease. [27]

There are further reports on autoimmunity after COVID-19 vaccination, mostly in the first two weeks following immunization, and some of them presented with early positivity for pathogenic autoantibodies. This indicates that COVID-19 vaccines may trigger overt autoimmunity in susceptible individuals or in patients with latent autoimmunity, possibly by priming autoreactive T and B cells. Case reports of autoimmunity were the following: cold agglutinin disease, aplastic anemia, reactive arthritis immune complex vasculitis, IgA vasculitis and Behcet disease flare, SLE, Polymyositis, relapse of microscopic polyangiitis, Giant Cell Arteritis. [45]

Sweet Syndrome (SS), also known as "acute febrile neutrophilic dermatosis" as firstly described in 1964 by Dr. Robert Douglas Sweet is an inflammatory disease, not categorized as an IMIDs, but with whom rheumatologists may encounter given the clinical presentation of fever, erythematous rashes and important biologic inflammatory syndrome. Additionally, SS can occur associated with a variety of IMIDs like RA, SLE, Sjogren's syndrome , mixed connective tissue disease etc. Recent reports show that SS can be triggered by SARS-CoV2 vaccination and clinicians should pay careful attention in regards to the treatment of this syndrome. [13]

3.7.2.5. Breakthrough infections in individuals with rheumatic disease.

Waning immunity has increased the number of breakthrough infections, immunosuppressive therapy being the risk factor with the greatest impact. [46] Data from the EULAR COVID-19 and COVAX registry suggest that breakthrough rates are low (<1%) in fully vaccinated individuals with inflammatory IMIDs. Nonetheless, there are two studies cited in our review that showed vaccine effectiveness for prevention of symptomatic COVID-19 in those on immunosuppression therapy was 71% and 62,9% compared to 94% and 91,3% in immunocompetent individuals. [27]

3.8. The role of intensive/extensive digitalization and A.I. in the pandemic and IMIDs

Nowadays, personalized medicine relies on advanced digital algorithms – machine learning (ML) and A.I. artificial intelligence (A.I.) – that can utilize and manipulate big complex data. A literature review conducted by Peng et. al revealed that ML can have various implications in the interference between the pandemic and IMIDs.

Thereby, the main practical application of ML is for drug development. More specifically, a model based on deep learning techniques and algebraic topology identified 71 covalent bonding inhibitors for SARS-CoV-2 main protease as a favorable drug target of SARS-CoV-2. BenevolentAI is the study where applied A.I. algorithms were used to explore potential treatment options for COVID-19 using existing anticytokine therapies. Such treatment option was studied for Baricitinib which was predicted to have an anti-viral (COVID-19) effect by the BenevolentAI algorithms. The beneficial effect of this drug was then observed in further studies in-vitro and in-vivo and after approval, in clinical practice, making A.I. a useful tool in this respect.

In IMIDs, ML techniques were successfully used for identifying MTX-induced liver toxicity in RA patients, predicting drug efficiency and molecular signatures predictive of response to ADA and etanercept, to predict SLE activity using gene expression data, to identify high disease activity SLE patients - using simple demographic and laboratory measurements, aiming to predict the risk of chronic damage in SLE patients - using longitudinal clinical and laboratory measurements. One 2019 SLE study draw our attention - researchers applied a ML model to enhance current neuropsychiatric SLE (NPSLE) diagnosis approaches based on resting-state functional connectivity MRI (fMRI) imaging data of the brain. The model achieved great performance, successfully identifying NPSLE patients and indicated that the frontoparietal brain region contributed most to the performance. [47,48]

4. Discussion

COVID-19 is a challenging and polymorph disease that can have devastating consequences, especially for patients with immune-mediated rheumatic diseases. Many actual related data emphasize that patients with IMIDs are at increased risk of hospitalization, and potentially of other severe outcomes of COVID-19. Mortality risk was associated with age, comorbidity and glucocorticoid use (≥10 mg prednisone- equivalent daily), disease activity at the time of COVID-19 diagnosis, therapy with RTX and SSZ.

In concern of new-onset or flares of rheumatic disease after COVID-19, there are case reports in the literature regarding SLE, RA, AS etc. where as many more situations - cases of flare-ups and new-onset rheumatic diseases were reported after SARS-CoV2 vaccination. However, significant cohorts of patients revealed that there is no difference in the flare-up percentage in people vaccinated against SARS-CoV2 versus patients unvaccinated. With respect to the type of DMARD used for treating the IMIDs - "the good" is anti-tumor necrosis factor α, "the bad" – MTX, SSZ, AZA and "the ugly" – anti CD20 monoclonal antibodies (widely used Rituximab). Moreover, there are multiple studies that link therapy with RTX as a risk factor for mortality in patients with IMID. Interestingly, the scientific medical team tested with great success anti-rheumatic drugs that are used as potential treatment for COVID-19 in non-rheumatic patients, like Hydroxychloroquine, Tocilizumab, Baricitinib and Anakinra.

Nowadays, even when WHO revoked the "pandemic" umbrella, given to the fact that the infectivity rate is not that high, a new health problem remains - Long COVID patients that experience a variety of symptoms that can be related to a rheumatic disease. The difficulty in diagnosis is higher for some patients that also present with autoantibodies – frequently transient in the evolution of the disease if we are talking about long COVID.

Vaccination against SARS-CoV2 in patients with IMIDs has its limitations and there are some particularities regarding its indication, timing of the immunomodulatory and immunosuppressive therapy and vaccine administration. For patients with IMIDs, mRNA vector vaccines are recommended over the others, they seem to be well tolerated, with low percentage of flare ups and with the same frequency of adverse effects as in the general population. The most problematic disease that impairs the immune response of the vaccine is SLE given the pathogenic down-regulation of the IFN 1 axis by the disease itself and impaired lymphocyte functions.

5. Conclusions

This extensive systematic literature review synthesizes the current findings regarding the COVID-19 impact on patients with IMIDs, focusing extensively on antibodies and cytokine profile at the intersection of IMIDs and SARS-CoV2, the gender role, its clinical and biological impact in IMIDs patients, new-onset and flares of such pathology after SARS-CoV2 infection, immunomodulators and immunosuppressive agents in the setting of COVID-19, long COVID cases, vaccination against SARS-CoV2 with implications in patients with IMIDs (concerning the disease and therapies used) and last but not least the role of A.I. in the pandemic and IMIDs.

This literature review is the part of the doctoral study that focuses on the same topics, with the current aim of deepening insights about the aspects at the intersection of COVID-19 and immune-mediated rheumatic diseases. As future perspectives we want to compare information we herein synthetized with our database of almost 170 Romanian patients with an IMID and COVID-19. Hence, the next objective is to extend the study to a multicenter control study.

As it could be determined, in a quite short time – since the onset of the pandemic – a lot of related data accumulated with predominantly useful knowledge and decision-makings, but with still not few items (some of them important) to be further approached and hopefully clarified.

6. Author Contributions

All authors made specific but overall equal contributions to this article.

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10. Conflict of interest

The authors declare no conflict of interest.

References

1. Tang KT, Hsu BC, Chen DY. Autoimmune and Rheumatic Manifestations Associated With COVID-19 in Adults: An Updated Systematic Review. Front Immunol. 2021 Mar 12;12.
2. Number of COVID-19 Patients. https://www.worldometers.info/coronavirus/.
3. Kaklamanos A, Belogiannis K, Skendros P, Gorgoulis VG, Vlachoyiannopoulos PG, Tzioufas AG. COVID-19 Immunobiology: Lessons Learned, New Questions Arise. Front Immunol. 2021 Aug 26;12.
4. Neurath MF. COVID-19: biologic and immunosuppressive therapy in gastroenterology and hepatology. Nat Rev Gastroenterol Hepatol. 2021 Oct 29;18(10):705–15.
5. McInnes IB, Gravallese EM. Immune-mediated inflammatory disease therapeutics: past, present and future. Nat Rev Immunol. 2021 Oct 13;21(10):680–6.
6. Patel NJ, D' Silva KM, Hsu TY, DiIorio M, Fu X, Cook C, et al. Coronavirus Disease 2019 Outcomes Among Recipients of <scp>Anti‐CD20</scp> Monoclonal Antibodies for <scp>Immune‐Mediated</scp> Diseases: A Comparative Cohort Study. ACR Open Rheumatol. 2022 Mar 10;4(3):238–46.
7. Curtis JR, Johnson SR, Anthony DD, Arasaratnam RJ, Baden LR, Bass AR, et al. American College of Rheumatology Guidance for <scp>COVID</scp>‐19 Vaccination in Patients With Rheumatic and Musculoskeletal Diseases: Version 4. Arthritis & Rheumatology. 2022 May 26;74(5).
8. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021 Mar 29;n160.
9. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009 Jul 21;6(7):e1000097.
10. PEDro score – Strokengine. https://strokengine.ca/glossary/pedro--score/ .
11. Onose G, Popescu N, Munteanu C, Ciobanu V, Sporea C, Mirea MD, et al. Mobile Mechatronic/Robotic Orthotic Devices to Assist–Rehabilitate Neuromotor Impairments in the Upper Limb: A Systematic and Synthetic Review. Front Neurosci. 2018 Sep 5;12.
12. 'Onose G, 'Stănescu-Răutzoiu L, 'Pompilian VM. Spondilartropatiile. Volume 1. Vol. 1. București: Editura Academiei Române; 2000. 28–32 p.
13. Joshi TP, Friske SK, Hsiou DA, Duvic M. New Practical Aspects of Sweet Syndrome. Am J Clin Dermatol. 2022 May 14;23(3):301–18.
14. Upasani V, Rodenhuis-Zybert I, Cantaert T. Antibody-independent functions of B cells during viral infections. PLoS Pathog. 2021 Jul 22;17(7):e1009708.
15. Morris G, Bortolasci CC, Puri BK, Marx W, O'Neil A, Athan E, et al. The cytokine storms of COVID-19, H1N1 influenza, CRS and MAS compared. Can one sized treatment fit all? Cytokine. 2021 Aug;144:155593.
16. Menzel A, Samouda H, Dohet F, Loap S, Ellulu MS, Bohn T. Common and Novel Markers for Measuring Inflammation and Oxidative Stress Ex Vivo in Research and Clinical Practice—Which to Use Regarding Disease Outcomes? Antioxidants. 2021 Mar 9;10(3):414.
17. Sheu TT, Chiang BL. Lymphopenia, Lymphopenia-Induced Proliferation, and Autoimmunity. Int J Mol Sci. 2021 Apr 16;22(8):4152.
18. Bezemer GFG, Garssen J. TLR9 and COVID-19: A Multidisciplinary Theory of a Multifaceted Therapeutic Target. Front Pharmacol. 2021 Jan 15;11.
19. 'West S, 'Kolfenbach J. Rheumatology Secrets. Elsevier; 2020. 27–29 p.
20. Fernández-Lázaro D, Sánchez-Serrano N, Mielgo-Ayuso J, García-Hernández JL, González-Bernal JJ, Seco-Calvo J. Long COVID a New Derivative in the Chaos of SARS-CoV-2 Infection: The Emergent Pandemic? J Clin Med. 2021 Dec 11;10(24):5799.
21. Singh P, Ali SA. Multifunctional Role of S100 Protein Family in the Immune System: An Update. Cells. 2022 Jul 23;11(15):2274.
22. Youness A, Miquel CH, Guéry JC. Escape from X Chromosome Inactivation and the Female Predominance in Autoimmune Diseases. Int J Mol Sci. 2021 Jan 23;22(3):1114.

23. Maranini B, Bortoluzzi A, Silvagni E, Govoni M. Focus on Sex and Gender: What We Need to Know in the Management of Rheumatoid Arthritis. J Pers Med. 2022 Mar 20;12(3):499.
24. 'West S, 'Kolfenbach J. Rheumatology Secrets. Elsevier; 2020. 133–134 p.
25. Mehta P, Machado PM, Gupta L. Understanding and managing anti-MDA 5 dermatomyositis, including potential COVID-19 mimicry. Rheumatol Int. 2021 Jun 27;41(6):1021–36.
26. Balcom EF, Nath A, Power C. Acute and chronic neurological disorders in COVID-19: potential mechanisms of disease. Brain. 2021 Dec 31;144(12):3576–88.
27. Grainger R, Kim AHJ, Conway R, Yazdany J, Robinson PC. COVID-19 in people with rheumatic diseases: risks, outcomes, treatment considerations. Nat Rev Rheumatol. 2022 Apr 25;18(4):191–204.
28. Radu AF, Bungau SG. Management of Rheumatoid Arthritis: An Overview. Cells. 2021 Oct 23;10(11):2857.
29. Mageau A, Papo T, Ruckly S, Strukov A, van Gysel D, Sacre K, et al. Survival after COVID-19-associated organ failure among inpatients with systemic lupus erythematosus in France: a nationwide study. Ann Rheum Dis. 2022 Apr;81(4):569–74.
30. Dima A, Jurcut C, Chasset F, Felten R, Arnaud L. Hydroxychloroquine in systemic lupus erythematosus: overview of current knowledge. Ther Adv Musculoskelet Dis. 2022 Jan 14;14:1759720X2110730.
31. García-Lledó A, Gómez-Pavón J, González del Castillo J, Hernández-Sampelayo T, Martín-Delgado MC, Martín Sánchez FJ, et al. Pharmacological treatment of COVID-19: an opinion paper. Revista Española de Quimioterapia. 2022 Mar 14;35(2):115–30.
32. Wang X, Lei J, Li Z, Yan L. Potential Effects of Coronaviruses on the Liver: An Update. Front Med (Lausanne). 2021 Sep 27;8.
33. Levy G, Guglielmelli P, Langmuir P, Constantinescu SN. JAK inhibitors and COVID-19. J Immunother Cancer. 2022 Apr;10(4):e002838.
34. Zhang Q, Li L, Chen H, Zhang G, Zhu S, Kong R, et al. Soluble urokinase plasminogen activator receptor associates with higher risk, advanced disease severity as well as inflammation, and might serve as a prognostic biomarker of severe acute pancreatitis. J Clin Lab Anal. 2020 Mar;34(3).
35. Giannini S, Giusti A, Minisola S, Napoli N, Passeri G, Rossini M, et al. The Immunologic Profile of Vitamin D and Its Role in Different Immune-Mediated Diseases: An Expert Opinion. Nutrients. 2022 Jan 21;14(3):473.
36. Sapkota HR, Nune A. Long COVID from rheumatology perspective — a narrative review. Clin Rheumatol. 2022 Feb 30;41(2):337–48.
37. D'Amelio R, Asero R, Cassatella MA, Laganà B, Lunardi C, Migliorini P, et al. Anti-COVID-19 Vaccination in Patients with Autoimmune-Autoinflammatory Disorders and Primary/Secondary Immunodeficiencies: The Position of the Task Force on Behalf of the Italian Immunological Societies. Biomedicines. 2021 Sep 4;9(9):1163.
38. Seirafianpour F, Pourriyahi H, Gholizadeh Mesgarha M, Pour Mohammad A, Shaka Z, Goodarzi A. A systematic review on mucocutaneous presentations after COVID‐19 vaccination and expert recommendations about vaccination of important immune‐mediated dermatologic disorders. Dermatol Ther. 2022 Jun 11;35(6).
39. Mohseni Afshar Z, Babazadeh A, Janbakhsh A, Mansouri F, Sio TT, Sullman MJM, et al. Coronavirus disease 2019 (Covid‐19) vaccination recommendations in special populations and patients with existing comorbidities. Rev Med Virol. 2022 May 22;32(3).
40. Qin S, Tang X, Chen Y, Chen K, Fan N, Xiao W, et al. mRNA-based therapeutics: powerful and versatile tools to combat diseases. Signal Transduct Target Ther. 2022 May 21;7(1):166.
41. Ferri C, Ursini F, Gragnani L, Raimondo V, Giuggioli D, Foti R, et al. Impaired immunogenicity to COVID-19 vaccines in autoimmune systemic diseases. High prevalence of non-response in different patients' subgroups. J Autoimmun. 2021 Dec;125:102744.
42. Magliulo D, Wade SD, Kyttaris VC. Immunogenicity of SARS-CoV-2 vaccination in rituximab-treated patients: Effect of timing and immunologic parameters. Clinical Immunology. 2022 Jan;234:108897.
43. Moyon Q, Sterlin D, Miyara M, Anna F, Mathian A, Lhote R, et al. BNT162b2 vaccine-induced humoral and cellular responses against SARS-CoV-2 variants in systemic lupus erythematosus. Ann Rheum Dis. 2022 Apr;81(4):575–83.
44. Hachulla E, Agard C, Allanore Y, Avouac J, Bader-Meunier B, Belot A, et al. French recommendations for the management of systemic sclerosis. Orphanet J Rare Dis. 2021 Jul 26;16(S2):322.
45. Camacho-Domínguez L, Rodríguez Y, Polo F, Restrepo Gutierrez JC, Zapata E, Rojas M, et al. COVID-19 vaccine and autoimmunity. A new case of autoimmune hepatitis and review of the literature. J Transl Autoimmun. 2022;5:100140.
46. Stevens KI, Frangou E, Shin JI l, Anders HJ, Bruchfeld A, Schönermarck U, et al. Perspective on COVID-19 vaccination in patients with immune-mediated kidney diseases: consensus statements from the ERA-IWG and EUVAS. Nephrology Dialysis Transplantation. 2022 Jul 26;37(8):1400–10.
47. Peng J, Jury EC, Dönnes P, Ciurtin C. Machine Learning Techniques for Personalised Medicine Approaches in Immune-Mediated Chronic Inflammatory Diseases: Applications and Challenges. Front Pharmacol. 2021 Sep 30;12.
48. Andritoi, D., Luca, C., Onu, I., Corciova, C., Fuior, R., Salceanu, A., & Iordan, D. A. (2022). The Use of Modern Technologies in Post-COVID-19 Cardiopulmonary Rehabilitation. Applied Sciences, 12(15), 7471.